Intraperitoneal Chemotherapy

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In 1955, Weissberger et al reported the results of intraperitoneal nitrogen mustard treatment of seven patients with ovarian cancer. Impressive control of malignant ascites accumulation was noted. Unfortunately, this study and other early clinical investigations of intraperitoneal drug administration were unable to demonstrate any impact of this therapeutic approach on intra-abdominal tumor masses, and the toxicity of the procedure was substantial, principally abdominal pain. Based upon these disappointing early experiences, intraperitoneal cytotoxic drug administration was rarely employed in the management of patients with ovarian cancer, except in those situations where one hoped to prevent ascites formation by producing cavity inflammation and subsequent sclerosis.

However, in the late 1970s, Dedrick and his colleagues at the National Cancer Institute (Bethesda, MD) described a mathematical model, based on known physiologic and anatomic characteristics of the peritoneal cavity as well as on previously reported pharmacokinetic data for certain chemotherapeutic agents, which suggested that the peritoneal cavity would be exposed to significantly more drug than the systemic circulation following the direct intraperitoneal administration of the agents. This model generated considerable interest as it hypothesized that tumor present within the peritoneal cavity might come in contact with two to three logs higher concentrations of drug than could be achieved with systemic delivery of the same agent.

In ovarian cancer, a tumor that remains largely confined to the peritoneal cavity for most of its natural history, there is both experimental and clinical evidence for a fairly steep cytotoxic dose-response curve to a number of chemotherapeutic agents. Thus, it can reasonably be theorized that the higher concentrations of drug achievable within the peritoneal cavity following intraperitoneal delivery might be translated into improved clinical response rates and survival in this malignancy.

Over the past decade investigators at several institutions have helped define the potential benefits and limitations of intraperitoneal drug administration in the management of ovarian cancer. A number of important principles have been established that clinicians should be familiar with prior to considering a particular patient or group of patients as appropriate candidates for treatment by the intraperitoneal route. At present, some of these principles can be generalized to all intraperitoneal treatment regimens, whereas others apply only to specific intraperitoneal programs.

Principles of Intraperitoneal Cytotoxic Drug Delivery in the Management of Ovarian Cancer

Adequacy of Drug Distribution

As any advantage of intraperitoneal administration over systemic delivery of the agent relies on free-surface diffusion of the drug into tumor cells, it is critical that the drug actually reach the site of tumor within the peritoneal cavity. Both experimental and clinical observations have demonstrated that large treatment volumes must be employed to maximize the opportunity to accomplish this goal. In most patients a treatment volume of ≥2 liters should be employed although it may be necessary in patients with a body surface area of less than 1.5 m² to treat with a somewhat lower volume. When a multiple day treatment program is utilized it is usually necessary to use a lower daily volume to prevent the patient from becoming excessively uncomfortable from the amount of fluid present in the cavity.

Unfortunately, although it is theoretically possible to remove fluid from the cavity prior to each treatment, greater than 50% of all surgically-implanted indwelling catheters (commonly employed to facilitate intraperitoneal...
drug administration) will ultimately develop "one-way valves," making it possible to easily administer treatment but not to remove fluid from the cavity following drug instillation.  

Limited Penetration of Drugs Into Tumor Tissue  
Perhaps the major factor determining the theoretical and practical limitations of intraperitoneal (IP) therapy in the management of ovarian cancer is the depth of penetration of cytotoxic agents directly into tumor. This issue has been examined both in vitro and in vivo in several experimental systems employing multiple agents with known activity against ovarian cancer. The universal conclusion of such studies has been that the direct penetration of the drugs into tissue is extremely limited, ranging from several cell layers to perhaps 1 to 3 millimeters from the tumor surface. 

Even more important than the absolute depth of penetration of drugs into tumor nodules is the relative advantage for drug delivery to the tumor following IP instillation compared to that achieved by systemic drug administration. It is possible that even with the high concentrations achieved locally following intraperitoneal delivery, similar levels may be observed after systemic drug delivery with the agent reaching tumor by capillary flow. In one experimental system examining this critical issue for cisplatin, the relative advantage of IP drug administration (compared to systemic delivery) was found to be limited to 0.1 to 1 mm from the peritoneal surface. 
Thus, we should not be surprised to find, as will be discussed later in this article, that any "superiority" of intraperitoneal cisplatin administration over intravenous delivery in refractory ovarian cancer will be limited to those patients with very small tumor volumes when intraperitoneal treatment is initiated.

Degree of Systemic Drug Exposure Following Intraperitoneal Administration  
One of the major criticisms of intraperitoneal treatment is the concern that despite the high local drug concentrations achieved with direct cavity delivery, the overall efficacy of therapy may be compromised if systemic drug exposure is inadequate with less drug being delivered to the tumor through the capillary system.

The dose limiting toxicities of drugs administered by the intraperitoneal route will be either systemic (ie, marrow suppression, mucositis, etc) or local (ie, abdominal pain, bowel obstruction, etc). If systemic side effects limit the amount of drug that can be delivered into the peritoneal cavity, it can reasonably be argued that the systemic exposure to the active drug (from entry of the agent into the systemic compartment) will approximate that achieved with intravenous administration of the drug. Conversely, if local effects of the agent limit the amount that can be delivered into the peritoneal cavity, systemic exposure may be far less than that attained following intravenous administration of the drug.

Therefore, the delivery of cytotoxic agents to tumor by capillary flow following intraperitoneal administration will be greatly influenced by the agents selected. For example, the intraperitoneal delivery of cisplatin or carboplatin results in minimal local toxicity, with systemic side effects limiting the amount of drug that can be delivered. Thus, there should be essentially no compromise in the amount of drug reaching tumor by capillary flow when either of these two drugs is administered by the intraperitoneal route, assuming doses that produce comparable systemic toxicities following intravenous administration are employed. However, if drugs such as doxorubicin, mitoxantrone, or mitomycin are instilled into the peritoneal cavity, there will be minimal systemic exposure due to the dose-limiting local toxic effects of these agents.

Limited Ability of Intraperitoneal Drug Delivery to Overcome Drug Resistance  
As previously noted, an important justification for the use of intraperitoneal chemotherapy in the management of ovarian cancer is the potential for overcoming drug resistance by significantly increasing the exposure of tumor to the cytotoxic agent. While there is major experimental support for the concept of concentration-dependent tumor cytotoxicity, particularly for agents such as cisplatin, the data clearly suggest that any increase in antineoplastic activity following intraperitoneal delivery compared to systemic drug administration will be relative rather than absolute.
Thus, if a tumor is highly resistant to a particular chemotherapeutic agent (i.e., tumor growth following intravenous delivery of appropriate doses of cisplatin-based therapy), there is little reason to believe delivering the drug into the peritoneal cavity will significantly improve tumor cell kill. Conversely, if a tumor has demonstrated sensitivity to an intravenously administered cytotoxic agent (i.e., initial microscopic tumor converted to microscopic residual disease confirmed at second look laparotomy), it is reasonable to speculate that the increased exposure achieved with intraperitoneal therapy employing the same or similar agents may lead to more tumor cell kill than could be accomplished by continuing with systemic therapy. This would be a major justification for employing second-line intraperitoneal cisplatin or carboplatin-based therapy in patients with small volume residual ovarian cancer (microscopic disease or tumor nodules < 0.5 to 1 cm) who have previously demonstrated a response to systemically administered cisplatin or carboplatin. Patients who have progressed or demonstrated minimal response to intravenous therapy with cisplatin or carboplatin, despite the presence of small volume disease at second look laparotomy (with or without secondary debulking), would be anticipated to experience limited benefit from the use of the intraperitoneal route to deliver these agents.

**Clinical Trials of Intraperitoneal Therapy in the Management of Ovarian Cancer**

Since the early 1980s, numerous conventional and experimental chemotherapeutic and biological agents have been examined for their safety and pharmacokinetic advantage following intraperitoneal drug delivery (Table 1). The mathematical model of Dedrick and his colleagues has turned out to be remarkably accurate in predicting the pharmacokinetic properties of antineoplastic drugs administered into the peritoneal cavity. Perhaps most impressive has been the advantage for cavity exposure for agents that are known to be metabolized during first passage through the liver (i.e., 5-FU, doxorubicin) and for drugs which appear to be deposited in tissue and demonstrate limited clearance into the systemic compartment (i.e., mitoxantrone).

As would have been anticipated, cisplatin has been the agent most extensively examined as intraperitoneal therapy of ovarian cancer. Despite the limited pharmacokinetic advantage for the intraperitoneal delivery of cisplatin, certainly compared to other cytotoxic agents (Table 1), the peritoneal cavity is exposed to 10 to 20 times more drug than the systemic compartment following intraperitoneal administration. In addition, a number of clinical trials have confirmed that the intraperitoneal instillation of cisplatin is associated with minimal local toxicity (pain, adhesion formation).

Several phase II intraperitoneal trials of single agent cisplatin or cisplatin-based combination therapy have been reported in patients with refractory or recurrent ovarian cancer (Table 2). The results of these trials are summarized in Table 3. To date, there are no reported random-
ized trials comparing single agent cisplatin (with or without thiosulfate nephroprotection) to cisplatin-based combination therapy or to alternative treatments as second-line therapy of ovarian cancer. Therefore, the objective response rates documented in these trials, impressive though they may be in small volume refractory or recurrent ovarian cancer, must be interpreted with caution. Of particular concern is the fact that patient selection bias (ie, treatment limited to individuals with responsive tumors, very small volume residual disease), although appropriate for deciding an individual patient is a reasonable candidate for an intraperitoneal approach, may make it difficult to compare these results to nonrandomized trials of alternative treatment strategies.

Despite these important limitations, it is reasonable to examine available data to obtain a preliminary assessment of whether there may be an advantage associated with second-line intraperitoneal cisplatin-based therapy compared to continued treatment with cisplatin or carboplatin delivered systemically. A retrospective analysis of three reported trials involving a total of 35 patients with ovarian cancer treated with five or six additional cycles of intravenous cisplatin following an initial partial response, revealed a surgically-defined complete response rate of 9%\textsuperscript{21,23} Pooling the results of five reported phase 2 trials of intraperitoneal cisplatin-based treatment of refractory/persistent ovarian cancer reveals a surgical complete response rate of 27% (33 of 122 patients) \textit{(P < 0.025)}\textsuperscript{5,24,27} This analysis suggests, although certainly does not prove, that there may be an advantage associated with the use of second-line cisplatin-based intraperitoneal therapy in patients demonstrating an initial response to systemically delivered cisplatin or carboplatin.

Even more difficult to evaluate is the impact on survival of cisplatin-based intraperitoneal therapy. In one retrospective analysis, a group of 25 patients with refractory or recurrent ovarian cancer with “small volume” disease (<2 cm) at the initiation of one of several intraperitoneal cisplatin-cytarabine-based phase 1 trials was reported to have experienced a 70% actuarial survival at 4 years following therapy.\textsuperscript{28}

While this and other reports of survival following intraperitoneal treatment are encouraging,\textsuperscript{29,30} the known extreme heterogeneity of survival for patients with residual ovarian cancer following front-line chemotherapy makes it difficult to interpret three or even 5-year survival figures in this clinical setting. For example, several reported series of patients with microscopic residual ovarian cancer at second-look laparotomy have noted 50% to 60% of patients surviving at 3 to 5 years following documentation of persistent disease.\textsuperscript{19,33}

Thus, randomized controlled clinical trials will be required to examine the impact on survival of second-line intraperitoneal or alternative innovative treatment strategies in ovarian cancer, unless a dramatic difference from the anticipated survival of the patient population is observed in phase 2 studies.

Several additional drugs have been examined for activity when administered by the intraperitoneal route in refractory/persistent ovarian cancer, including carboplatin,\textsuperscript{34} 5-FU,\textsuperscript{35} mitoxantrone,\textsuperscript{36} and mitomycin.\textsuperscript{19}

Mitoxantrone is of particular interest for intraperitoneal delivery as preclinical evaluation has demonstrated it produces a profound cytotoxic effect against ovarian cancer cells at concentrations of the agent achievable following intraperitoneal instillation but not with systemic delivery.\textsuperscript{4,18} A recently reported phase 2 trial of mitoxantrone in refractory ovarian cancer has demonstrated surgically-defined activity, including responses in patients previously failing intraperitoneal cisplatin.\textsuperscript{18} Unfortunately, the drug was found to produce excessive local toxicity (abdominal pain, bowel obstruction) at the doses administered in this trial (20 mg/m\textsuperscript{2} or 30 mg/m\textsuperscript{2}) and its use cannot be recommended at the present time in the standard management of patients with ovarian can-
cancer. Investigators at several centers are attempting to reduce the local toxicity of mitoxantrone while maintaining therapeutic efficacy by delivering the drug at lower concentrations or adding orally administered nonsteroidal anti-inflammatory agents to the therapeutic regimen.

It should also be noted that biological agents have been examined for safety and efficacy when administered by the intraperitoneal route in patients with ovarian cancer. The rationale for this approach includes both direct concentration-dependent cytotoxicity of the biologicals, as well as the potential stimulation of local immune mechanisms to produce tumor cell kill. Due to the large size of the biological agents, significant concentrations persist in the cavity for greater than 24 hours following intraperitoneal instillation, in contrast to the smaller chemotherapeutic agents whose half-lives in the peritoneal cavity are generally less than several hours. Both recombinant interferon alfa and interleukin-2 have demonstrated activity against small volume residual ovarian cancer when administered intraperitoneally in phase 1-2 trials. Recombinant interferon gamma delivered by the intraperitoneal route has also been shown in one report to be quite active in ovarian cancer, whereas a second study using a lower dose of the agent has failed to demonstrate activity.

A Role for Intraperitoneal Therapy in the Management of Ovarian Cancer

After a decade of active clinical research with intraperitoneal therapy in ovarian cancer, what can be said about its role in the standard management of this disease?

In one clinical setting, based on available clinical data, it is reasonable to suggest that intraperitoneal therapy is an acceptable “standard treatment” option in patient management (Table 4): Patients with persistent minimal residual ovarian cancer (microscopic disease or ≤ 0.5 cm lesions) following initial intravenous cisplatin or carboplatin-based chemotherapy who have demonstrated a response to the systemically delivered regimen are appropriate candidates for an intraperitoneal cisplatin/carboplatin treatment program. No alternative strategy has yielded superior clinical results and a subset of patients treated with this approach appear to experience prolonged (> 2 to 4 year) disease-free survival.

As of this date, the use of intraperitoneal therapy in other clinical settings in ovarian cancer or intraperitoneal therapy with noncisplatin/ carboplatin regimens cannot be recommended as “standard practice”, simply due to the fact that there is inadequate data available to support the effectiveness of such a therapeutic strategy.

Several clinical situations where intraperitoneal therapy may play a role in the management of ovarian cancer are outlined in Table 4. In each case, randomized clinical trials will ultimately be required to show that the pharmacokinetic advantage for regional drug administration can be translated into a survival benefit for patients treated with this approach.

CONCLUSION

Intraperitoneal therapy of ovarian cancer has come a long way from its early days when locally toxic alkylating agents were instilled into the peritoneal cavity to control malignant ascites. The use of the technique is strongly supported by sound preclinical experimental data and clinical pharmacokinetic studies. In addition, phase 2 trials have demonstrated efficacy in patients with small volume disease. Future studies will need to examine new drugs (including biologicals) and drug combinations, and critically evaluate the clinical utility of this approach compared to alternative therapeutic strategies.
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REFERENCES


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